REMARKS

I. Status of the Claims

Prior to the present amendment, claims 1-92 were pending. Presently, claims 20-22, 24-50 and 53-92 have been canceled, without prejudice or disclaimer, but prior to calculation of the filing fee. No claims have been amended or added.

Claims 1-19, 23, 51 and 52 are therefore in the case. According to the revisions to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Support for the Amendment

This amendment is the first step in revising the claims so that the present application is directed to only one of the inventions originally claimed when the application was filed. Accordingly, many claims have been canceled without prejudice or disclaimer.

It will be understood that no new matter is introduced by the amendment.

The present amendment only cancels claims and is enterable prior to calculation of the filing fee under MPEP 714.01(e) and MPEP 506. According to MPEP 714.01(e), other amendments to the claims, specification and inventors will follow in a separate amendment document (MPEP 714.01(e) at page 700-195, column 1, Feb., 2003).

Although the present amendment did not accompany the application at the time of filing, it is expressly directed to reducing the number of claims prior to calculation of the filing fee. The amendment is proper under MPEP 506, as the amendment cancels claims as the first step in revising the claims so that the filing fee will be correct when submitted (MPEP 506 at page 500-19, column 2, Feb., 2003).

III. Conclusion

The amendment is properly enterable, being submitted promptly after filing the application, but before calculation of the filing fee by the Office. The amendment will not unduly interfere with calculation of the filing fee, let alone the preparation of a first Office Action. The changes will not require significant time for review or cause an undue burden.

The amendments is therefore both timely and proper and should be entered under MPEP 714.01(e), MPEP 506 and 37 C.F.R. § 1.115. No fees should be due until Applicants are notified of the filing fee. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4001.003000.

Should the Office have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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AMENDMENTS TO THE SPECIFICATION

In the inventors, please delete Melina Soares, Xianming Huang and Jin He from the listed inventors, so that only the proper inventors of the presently claimed invention, Philip E. Thorpe and Sophia Ran, remain listed on this application.

In the title, please delete the existing title and replace with the following title after implementing the following changes:

SELECTED ~~ANTIBODIES AND DURAMYCIN PEPTIDES BINDING TO ANIONIC PHOSPHOLIPIDS &~~ ANTIBODY COMPOSITIONS FOR BINDING TO AMINOPHOSPHOLIPIDS ~~AND THEIR USE IN TREATING VIRAL INFECTIONS AND CANCER~~

In the specification, at page 22, lines 14-17, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

All selection criteria, as used herein, are preferably conducted in the absence of serum, to avoid the drawbacks with generating antibodies that could ~~mimick~~ mimic the pathological antibodies of patients, which bind to aminophospholipids or anionic phospholipids in conjunction with proteins.

In the specification, at page 25, lines 20-23, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The cell impermeant group may have a positive or negative charge at physiological pH or may be polar. ~~Examplary~~ Exemplary groups include sulfate, sulfonate, phosphate, carboxyl,

phenolic, quaternary ammonium ion and amine groups. A pharmaceutical composition comprising duramycin linked to biotin is a particular example within the invention.

In the specification, at page 30, lines 26-32, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Combined cancer treatment methods are those in which at least a first purified anti-aminophospholipid or anti-anionic phospholipid antibody, or antigen-binding fragment or immunoconjugate thereof, optionally one that binds to essentially the same epitope as the monoclonal antibody 3G4 (ATCC PTA 4545), or a substantially cell impermeant PE-binding peptide derivative, preferably a substantially cell impermeant duramycin derivative, is administered to an animal or patient with cancer in ~~combiantino~~ combination with a therapeutically effective amount of at least a second, therapeutic or anti-cancer agent.

In the specification, at page 40, lines 20-26, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

FIG. 14A, FIG. 14B, FIG. 14C and FIG. 14D. Binding specificities of duramycin derivatives. The duramycin derivatives were prepared as described in Example XV and their specificities determined using ELISAs and competition ELISAs, as described in Example XVI. FIG. 14A, phospholipid binding profile of duramycin derivatives against a panel of phospholipids, showing specificity for PE; FIG. 14B, serum has no significant effect on PE binding; FIG. 14C and FIG. 14D, results from competition ELISAs ~~comfirming~~ confirming specificity of duramycin derivatives for PE.

In the specification, at page 58, lines 24-32, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

It is also possible that antibody binding to anionic phospholipids and aminophospholipids at the surface of tumor vascular endothelial cells may cause disturbances in the ~~cytoskeletalal~~ cytoskeletal organization of the cell. As the cytoskeleton plays a role in the organization of surface membranes, and as antibody binding may disturb (or further disturb) the membrane, binding of antibodies to anionic phospholipids and aminophospholipids may transmit changes to cytoskeletal proteins that interact with the bilayer. It is already known that the spatial organization of cytoskeletal proteins controls membrane stability and cell shape, and it is possible that perturbation of some cytoskeletal equilibrium may have far-reaching consequences on cell integrity.

In the specification, from page 63, line 33 to page 64, line 4, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The present invention provides "second generation" antibodies that bind to aminophospholipids and anionic phospholipids, which antibodies have improved properties and/or do not ~~suffere~~ suffer from the drawback associated with the antibodies in the prior art. A panel of such antibodies is disclosed herein, of which the monoclonal antibodies 9D2 and 3G4 are currently preferred, with the 3G4 (ATCC 4545) antibody being particularly preferred. The invention also provides particular immunization and screening techniques, which permit "like" or "competing" antibodies with advantageous properties and/or less drawbacks to be produced.

In the specification, at page 117, lines 18-23, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Depending on the specific agents to be conjugated, it may be necessary or desirable to provide a peptide spacer operatively attaching the antibody or PE-binding peptide and the second or therapeutic agent. ~~Cetain~~ Certain peptide spacers are capable of folding into a disulfide-bonded loop structure. Proteolytic cleavage within the loop would then yield a heterodimeric polypeptide wherein the antibody and the therapeutic agent are linked by only a single disulfide bond. An example of such a toxin is a Ricin A-chain toxin.

In the specification, from page 158, line 34 to page 159, line 4, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Drugs that induce apoptosis are preferred for use in the ~~combinaition~~ combination therapies. Docetaxel, for example, induces apoptosis and therefore PS exposure by binding to microtubules and disrupting cell mitosis (Hotchkiss *et al.*, 2002). Treatment of endothelial cells, which line tumor blood vessels, and tumor cells with docetaxel at subclinical concentrations is herein shown to induce PS expression at the cell surface, as demonstrated by strong binding of the 3G4 antibody *in vitro*.

In the specification, at page 176, lines 18-23, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Moreover, the antibody-coated stealthed liposomes of the invention may also be loaded with one or more anti-viral drugs for use in treating viral infections and diseases. As with the anti-cancer agents, any one or more of the second, anti-viral drugs known in the art and/or

described herein for conjugation to antibodies, or for combination therapies, may be used in the antibody-coated stealthed liposomes of the invention. ~~Cidofavir~~ Cidofovir and AZT are currently preferred examples.

In the specification, at page 182, lines 13-21, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Within this category of PE-binding peptide derivatives, certain constructs will emphasize the recruitment of host defenses, thus ~~enhacing~~ enhancing their therapeutic activity. For example, where a PE-binding peptide, preferably duramycin, is attached to an immunoglobulin, the immunoglobulin can function both as an inert carrier and as an immune effector. This applies to immunoglobulins of so-called "irrelevant specificity" and to immunoglobulin derivatives without antigen binding capacity, such as Fc regions. By virtue of the attached immunoglobulin or immunoglobulin derivative, such constructs will be able to redirect host defenses against PE-expressing cells, *e.g.* by attracting and/or activating immune effector cells.

In the specification, at page 183, lines 7-12, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Any of the conjugation techniques ~~decribed~~ described above may be used to prepare duramycin derivatives in accordance with the invention, including cross-linkers, peptide spacers, biotin:avidin constructs and recombinant expression. An advantageous site of attachment within the duramycin molecule, for example, is to the lysine residue at amino acid position 2 in the duramycin sequence (SEQ ID NO:9; FIG. 13P; Hayashi *et al.*, 1990). However, linkage at this site is not a requirement of the invention.

In the specification, at page 196, lines 10-14, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

As the PE-binding peptide derivatives localize to macrophages in the lung after systemic administration will naturally be effective. Administration to the lung by more direct means, including via aerosol, is also envisioned. The present invention therefore solves important deficiencies in the viral treatment field ~~bu~~ by providing widely applicable and practical anti-viral remedies.

In the specification, at page 279, lines 10-16, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The 3G4 antibody is also shown to be very effective in inhibiting CMV, both *in vitro* (Example XII) and in enhancing the survival of mice infected with mCMV *in vivo* (Example XXI). In addition, the 3G4 antibody is further shown to inhibit Pichinde virus infection, the infectious agent of Lassa fever (Example XXIV). The cell surface PS exposure herein shown to follow viral infection, and the ability of the 3G4 antibody to bind to cells infected with Vaccinia virus (Example XXIII), shows that the 3G4 antibody has enormous potential as a broad ~~spectum~~ spectrum anti-viral agent.

In the specification, at page 289, lines 15-23, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

Using the same MethA mouse tumor model as above, when the tumor size reach 500 mm^3, 100 μg $(D\text{-}SIAB)_nHIgG$ in 100 μl PBS was injected through the tail vein. The same

amount of human IgG was injected as a control. After 4 hours, mice was euthanized and perfused with normal saline for 5 minutes and 1% paraformadehyde for 10 minutes. The tumor and other major organs were dissected and frozen in liquid nitrogen. After embedding in OCT, tissue was cryosected in 10 μm section and placed on silanized slides. After fixing in cold acetone for 10 minutes, slides were stained with peroxidase labeled goat anti human IgG to ~~dectect~~ detect the biodistribution of duramycin-HuIgG. Meca32 and peroxidase labeled goat anti-rat IgG were used to detect blood vasculature of tissue.

In the specification, at page 290, lines 11-20, please delete the existing paragraph and replace with the following paragraph after implementing the following changes:

The human breast cancer cell line MDA-MB-435 was grown, harvested at log phase, and resuspended in DPBS. Approximately 10^7 cells were injected into the mammary fat pad of 6-8 week old female athymic nude mice. 100 μg duramycin-biotin in 100 μl PBS was injected through the tail vein. After 4 hours, mice was euthanized and perfused with normal saline for 5 minutes and 1% paraformadehyde for 10 minutes. Major organs, including heart, lung, liver, kidney, brain, intestine, testes and spleen were dissected and frozen in liquid nitrogen. After embedding in OCT, tissue was cryosected in 10 μm sections and placed on silanized slides. After fixing in cold acetone for 10 minutes, slides were stained with Cy3 labeled ~~strepavidin~~ streptavidin to ~~dectect~~ detect the biodistribution of the duramycin-biotin construct. Meca32 and FITC labeled goat anti rat IgG were used to detect blood vasculature of tissue.

AMENDMENTS TO THE CLAIMS

The present document amends claims 1, 16, 19 and 51, and adds claims 93-99. According to 37 C.F.R. § 1.121(c), after entry of the present amendment, the status of the claims in the case is as follows:

1. (Currently Amended) A composition comprising a purified antibody, or antigen-binding fragment ~~or immunoconjugate~~ thereof, wherein said antibody binds to phosphatidylserine and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylserine.

2. (Original) The composition of claim 1, wherein said antibody further binds to phosphatidic acid and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidic acid.

3. (Original) The composition of claim 1, wherein said antibody further binds to phosphatidylinositol and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylinositol.

4. (Original) The composition of claim 1, wherein said antibody further binds to phosphatidylglycerol and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylglycerol.

5. (Original) The composition of claim 1, wherein said antibody further binds to cardiolipin and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to cardiolipin.

6. (Original) The composition of claim 1, wherein said antibody further binds to phosphatidic acid, phosphatidylinositol, phosphatidylglycerol and cardiolipin and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to each of phosphatidic acid, phosphatidylinositol, phosphatidylglycerol and cardiolipin.

7. (Original) The composition of claim 1, wherein said antibody further binds to phosphatidylethanolamine.

8. (Original) The composition of claim 7, wherein said antibody further binds to phosphatidylethanolamine and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylethanolamine.

9. (Original) The composition of claim 1, wherein said antibody has substantially the same phospholipid binding profile as the monoclonal antibody 3G4 (ATCC PTA 4545) as set forth in Table 4.

10. (Original) The composition of claim 1, wherein said antibody has an affinity for phosphatidylserine of at least equal to the affinity of the monoclonal antibody 3G4 (ATCC PTA 4545) for phosphatidylserine as set forth in Table 3.

11. (Original) The composition of claim 1, wherein said antibody has substantially the same phospholipid binding profile as the monoclonal antibody 3G4 (ATCC PTA 4545), as set forth in Table 4, and has an affinity for phosphatidylserine of at least equal to the affinity of the monoclonal antibody 3G4 (ATCC PTA 4545) for phosphatidylserine, as set forth in Table 3.

12. (Original) The composition of claim 1, wherein said antibody is a monoclonal antibody or antigen-binding fragment thereof.

13. (Original) The composition of claim 1, wherein said antibody is an IgG antibody.

14. (Original) The composition of claim 1, wherein said antibody is an antigen-binding fragment of an antibody.

15. (Original) The composition of claim 14, wherein said antibody is an scFv, Fv, Fab', Fab, diabody, linear antibody or $F(ab')_2$ antigen-binding fragment of an antibody.

16. (Currently Amended) The composition of claim 14, wherein said antibody is a ~~CDR,~~ univalent fragment, camelized or single domain antibody.

17. (Original) The composition of claim 1, wherein said antibody is a human, humanized or part-human antibody or an antigen-binding fragment thereof.

18. (Original) The composition of claim 17, wherein said antibody comprises an antigen-binding region of said antibody operatively attached to a human antibody framework or constant region.

19. (Currently Amended) The composition of claim 1, wherein said antibody is a chimeric, bispecific, recombinant or engineered antibody.

Claims 20-22 canceled

23. (Original) The composition of claim 1, wherein said antibody is prepared by a process comprising immunizing an animal with activated endothelial cells and selecting from the immunized animal an antibody that binds to phosphatidylserine and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylserine.

Claims 24-50 canceled

51. (Currently Amended) The composition of claim 1, wherein said composition is a pharmaceutically acceptable composition ~~that further comprises a pharmaceutically acceptable carrier~~.

52. (Original) The composition of claim 51, wherein said pharmaceutically acceptable composition is formulated for parenteral administration.

Claims 53-92 canceled

93. (New) A composition comprising a purified anti-phosphatidylserine antibody, or antigen-binding fragment thereof, wherein said antibody binds to substantially the same epitope as the monoclonal antibody 3G4 (ATCC PTA 4545).

94. (New) A composition comprising a purified antibody that binds to phosphatidylserine and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylserine.

95. (New) An antibody, or antigen-binding fragment thereof, that binds to phosphatidylserine and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylserine, wherein said antibody is prepared by a process comprising immunizing an animal with activated endothelial cells and selecting from the immunized animal an antibody that binds to phosphatidylserine and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylserine.

96. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a biologically effective amount of a purified antibody, or antigen-binding fragment thereof, wherein said antibody binds to phosphatidylserine and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylserine.

97. (New) A purified antibody, or antigen-binding fragment thereof, wherein said antibody binds to phosphatidylserine and effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylserine.

98. (New) A hybridoma that produces a monoclonal antibody that effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylserine.

99. (New) A method for preparing an anti-phosphatidylserine antibody that binds to substantially the same epitope as the monoclonal antibody 3G4 (ATCC PTA 4545), comprising immunizing an animal with activated endothelial cells and selecting from the immunized animal an anti-phosphatidylserine antibody that effectively competes with the monoclonal antibody 3G4 (ATCC PTA 4545) for binding to phosphatidylserine.

REMARKS

I. Status of the Claims

Prior to the present amendment, claims 1-19, 23, 51 and 52 were pending. Claims 20-22, 24-50 and 53-92 were canceled in a separate amendment document to reduce the filing fee. Presently, claims 1, 16, 19 and 51 have been amended without prejudice or disclaimer. Claims 93-99 have been added, which are fully supported by the application as filed.

Claims 1-19, 23, 51, 52 and 93-99 are therefore in the case. According to the revisions to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Support for the Claims

Support for the revised and new claims exists throughout the specification and claims of the original application. The present claim amendments are the second step in revising the application so that it is directed to only one of the inventions originally claimed when the application was filed.

Within the pending claims, claim 1 has been revised so that the claims are directed only to antibodies with the claimed properties, not to immunoconjugates of such antibodies.

Claim 16 has been revised to remove CDR constructs.

In claim 19, the terms "bispecific, recombinant and engineered" have been added to further define the antibodies, as originally recited in claims 20, 21 and 22, which provide exemplary support.

Claim 51 has been revised to more succinctly define the claimed invention.

New claims 93-99 are additional independent claims, which are supported by the application as filed.

Claim 93 defines the antibody of the composition as one that "binds to substantially the same epitope as the monoclonal antibody 3G4 (ATCC PTA 4545)", which is supported by claim 1 and throughout the specification as filed.

New claim 94 is based upon claim 1, and is supported thereby, but does not include the antigen-binding fragment embodiment.

Claim 95 is a product-by-process claim, which is based upon claim 1 in combination with original claim 23.

New claim 96 is an independent claim directed to a pharmaceutical composition, which is supported by claim 1 in combination with original claim 51.

Claim 97 is an independent claim more particularly directed to the purified antibody, which is supported by claim 1 without the "composition comprising" language.

New claim 98 is directed to a hybridoma that produces the claimed antibody, which is supported by claim 1 and throughout the specification as filed.

Finally, claim 99 is a method claim directed to the preparation of the claimed antibody, which is supported by original claims 1 and 23 and throughout the specification as filed.

It will therefore be understood that no new matter is included within the pending claims.

III. Change in Inventorship

The inventors listed when the application was filed were the correct inventors for claims 1-92. In light of the changes to the claims, particularly the deletion of claims in the separate but concurrent amendment, the correct inventors for the presently claimed invention are Philip E. Thorpe and Sophia Ran. Accordingly, Melina Soares, Xianming Huang and Jin He are being removed from the listed inventors for the present application.

The present change in inventorship is proper under 37 C.F.R. § 1.48(f)(1) for a nonprovisional application filed without an executed oath or declaration.

IV. Amendments to the Specification

Amendments to the specification are also made in the amendment section. Such amendments correct typographical errors, the nature of which is evident in the amended paragraphs, and are supported by the specification as filed. No new matter is included within the amendments. The amendments comply with the revisions to 37 C.F.R. § 1.121.

V. Conclusion

The present amendment is submitted in a separate document to the amendment that cancels claims prior to calculation of the filing fee. This is proper under MPEP 714.01(e) and MPEP 506.

The amendment is thus enterable, being submitted promptly after filing the application, but also before calculation of the filing fee. The amendment will not unduly interfere with calculation of the filing fee, let alone the preparation of a first Office Action. The changes will not require significant time for review or cause an undue burden. Entry of the amendment is therefore proper under 37 C.F.R. § 1.115.

No fees should be due until Applicants are notified of the filing fee. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4001.003000.

Should the Office have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

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